

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12P 17/10, C07D 205/08	A1	(11) International Publication Number: WO 00/60107 (43) International Publication Date: 12 October 2000 (12.10.00)
<p>(21) International Application Number: PCT/US99/07445</p> <p>(22) International Filing Date: 5 April 1999 (05.04.99)</p> <p>(71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): HOMANN, Michael, J. [US/US]; 47 Quarry Ridge Road, Clinton, NJ 08809 (US). PREVITE, Edward [US/US]; 655A Cranbury Cross Road, North Brunswick, NJ 08902 (US).</p> <p>(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: STEREOSELECTIVE MICROBIAL REDUCTION FOR THE PREPARATION OF 1 - (4-FLUOROPHENYL) - 3(R)-[3(S) - HYDROXY-3 - (4-FLUOROPHENYL) PROPYL]-4(S) - (4-HYDROXYPHENYL)-2-AZETIDINONE</p>		
<p>(57) Abstract</p> <p>A process for the stereoselective microbial reduction of compound of formula (II) to compound of formula (I) comprising adding compound of formula (II) to a medium, medium and buffer, medium and solvent, or medium and a mixture of buffer and solvent containing a microorganism, preferably <i>Rhodococcus fascians</i> ATCC No.202210 or fungal isolate <i>Geotrichum candidum</i> ATCC No. 74487, incubating the resulting mixture, and isolating a hydroxy compound of formula (I), is described. The compound of formula (I) is a serum cholesterol lowering agent.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT:

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

5

10 **STEREOSELECTIVE MICROBIAL REDUCTION FOR THE
PREPARATION OF 1-(4-FLUOROPHENYL)-3(R) -[3(S)-
HYDROXY-3-(4-FLUOROPHENYL)PROPYL]-4(S)-(4-
HYDROXYPHENYL)-2-AZETIDINONE**

15 BACKGROUND OF THE INVENTION

1-(4-Fluorophenyl)-3(R) -[3(S)-hydroxy-3-(4-fluorophenyl)-
propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone is disclosed as a
cholesterol lowering agent in WO 95/08532, published March 30, 1995.
U.S. Patent 5,618,707 discloses stereoselective microbial reduction of a
20 keto intermediate (4-(4-fluoro-benzoyl)butyric acid or a
phenyloxazolidinone conjugate thereof) used in the preparation of the
azetidinone to the corresponding hydroxy intermediate using the
microorganism *Zygosaccharomyces bailii* or *Schizosaccharomyces*
octosporus.

25

SUMMARY OF THE INVENTION

The present invention relates to a process for the microbiological
reduction of carbonyl groups which comprises the use of
microorganisms (obtained from environmental sources and culture
30 collections, e.g., the American Type Culture Collection (ATCC)) in
medium, medium and buffer, medium and solvent, or medium and a
mixture of buffer and solvent to which a ketone compound can be added
so that a compound having a hydroxy group of desired stereochemistry
can be formed, accumulated and isolated.

35

In particular, the present invention relates to a process for the
stereoselective reduction of 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluoro-
phenyl)propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone to 1-(4-fluoro-

-2-

phenyl)-3(R) -[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxy-phenyl)-2-azetidinone comprising adding 1-(4-fluoro-phenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone to a microorganism in medium, medium and buffer, medium and solvent, or
5 medium and a mixture of buffer and solvent, incubating the resulting mixture, and isolating 1-(4-fluoro-phenyl)-3(R) -[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone.

Microorganisms selected from the group consisting of the following genera have been found to be useful in the reduction of this
10 invention: *Aspergillus*, *Curvularia*, *Doratomyces*, *Geotrichum*, *Mortierella*, *Mucor*, *Saccharomyces*, *Scytalidium*, *Pichia*, *Torulaspora*, *Neurospora* and *Rhodococcus*. The following species of the above genera are preferred: *Aspergillus niveus*, *Curvularia lunata*,
15 *Doratomyces stemonitis*, *Geotrichum candidum*, *Mortierella isabellina*, *Mucor racemosus* and *circinelloides*, *Saccharomyces cerevisiae* and *uvarum*, *Scytalidium lignicola*, *Pichia methanolitica*, *Torulaspora fermentati* and species, *Neurospora crassa* and *Rhodococcus erythropolis*, *fascians*, *rhodochrous* and species.

In particular, the present invention relates to a process for the
20 microbiological reduction of the carbonyl group of 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone (Formula II, below) comprising adding said compound to a microorganism in medium, medium and buffer, medium and solvent, or medium and a mixture of buffer and solvent, especially wherein the
25 microorganism is *Rhodococcus fascians* ATCC No. 202210 or fungal isolate *Geotrichum candidum* ATCC No. 74487, incubating the resulting mixture, and isolating 1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone (Formula I, below).

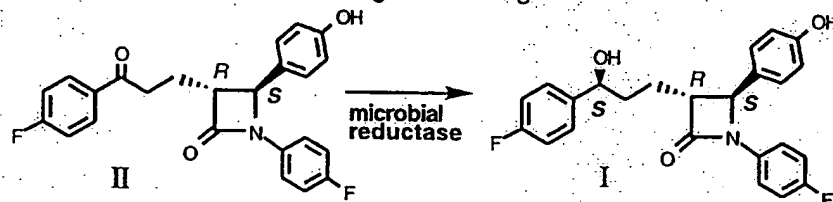
30 Viable cultures of the microorganism and the fungal isolate have been deposited in the collection of the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, where the microorganism has been assigned accession number ATCC 202210 and fungal isolate has been assigned accession number ATCC
35 74487. Should a deposited culture become lost, destroyed or non-

-3-

viable during the longer of the thirty (30) year period from the date the culture was deposited or the five (5) year period after the last request for the deposited culture or the effective life of the patent which issues from this application, the culture will be replaced, upon notice, by applicants or assignee(s) of this application. Subcultures of *Rhodococcus fascians* ATCC No. 202210 and *Geotrichum candidum* ATCC 74487 are available during the pendency of this application to one determined by the Commissioner of Patents and Trademarks to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. 122 and will be available to the public without restriction once a patent based on this application is granted. Use of the microorganism and fungal isolate is dependent on the US Patent Laws.

DETAILED DESCRIPTION

This invention relates to a method for performing the following stereospecific reduction using a microorganism.



The microbiological reduction is carried out by adding the ketone substrate of formula II, above, to medium, medium and buffer, medium and solvent, or medium and a mixture of buffer and solvent containing microorganisms. The incubation may be conducted at temperatures in the range from between about 20°C and about 40°C, preferably 30°C, while adjusting the initial pH value of the reaction in the range from between about 5.0 and about 9.0, preferably 7.0.

The initial concentration of compound II in the reaction may vary from between about 0.5 g/l and about 10.0 g/l, and is preferably 2-4.0 g/l.

Suitable fermentation media, buffers and solvents are known to those skilled in the art. Fermentation media typically contain a carbon and nitrogen source or mixtures thereof, using such ingredients as yeast extract, nutrient broth, dextrose (cerelose), white potato dextrin, soy flour, peptone and other components known in the art. Typical buffers are

-4-

phosphate buffer (e.g., 0.1 M at pH 7), MES (2-[N-morpholino]ethanesulfonic acid), Bis-Tris (bis[2-hydroxyethyl]iminotris[hydroxymethyl]methane), PIPES (1,4-piperazine-diethanesulfonic acid), HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), TRIS (tris(hydroxymethyl)aminomethane) and MOPS (3-[N-morpholino]propanesulfonic acid) buffer (e.g., 0.1 M at pH 7). Typical solvents are acetonitrile, acetone, ethyl ether, isopropanol, t-butanol, isoamyl alcohol, p-dioxane, isopropyl ether, dimethyl sulfoxide, t-butyl methyl ether (TBME), toluene, tetrahydrofuran and CH_2Cl_2 . Preferably, the microbial reduction is carried out in fermentation media.

The duration of the chiral reduction reaction may vary from about 18 to about 96 hours, and is preferably about 48-72 hours.

At the end of the reduction reaction, the hydroxy compound of formula I may be extracted by well known methods, using organic solvents such as ethyl acetate (EtOAc), t-butyl methyl ether (TBME), methylene chloride (CH_2Cl_2) and the like. Adsorption to resins, chromatography, and other physical methods known to the art may also be used to extract the hydroxy compound of formula I.

A large number of microorganisms were investigated to determine whether or not they reduce the ketone compound of formula II. Many such microorganisms failed to provide the desired specificity or productivity.

The examples below demonstrate the evaluation of microorganisms in the reduction of this invention and the preparation of milligram quantities of the hydroxy compound of formula I.

Example 1

The general method for identifying the stereoselective microbial reduction of the compound of formula II for use as a synthetic precursor for the production of the compound of formula I is described below.

Seed cultures of yeast, filamentous fungi, and bacteria were grown in 125 ml or 300 ml flasks containing 25 ml or 50 ml of YPD (1% yeast extract, 2% peptone, 2% dextrose; pH 5.5), SIM6 (3.5% soy flour, 5% white potato dextrin, 0.5% cerelose, 2 mg/l cobalt chloride, 0.5% calcium carbonate; pH 6.0) and NYC (0.8% nutrient broth, 2% yeast extract, 1.1% cerelose; pH 7.0) media, respectively, for 72 hours at 30°C with agitation (175-250 rpm) prior to inoculation (4 % v/v) into flask

-5-

- fermentations (25ml YPD/125 ml flask for yeast and filamentous fungi or 25ml NYC /125 ml flask for bacteria) which were incubated at 30°C with agitation (250 rpm). In all fermentations, medium pH was adjusted prior to inoculation but was not controlled during culture propagation and
- 5 ketone reduction. Reduction was initiated by adding 0.5-1.0 g/l of the ketone compound of formula II dissolved in ethanol (25 mg/ml) directly to cultures following 24 hours of growth. Samples of fermentation broth extracted with EtOAc (1:1) following 48 hours incubation with substrate were analyzed by reverse-phase HPLC. Cultures demonstrating
- 10 consistent reduction activity without significant substrate degradation following repeated fermentations using this procedure were further analyzed by chiral HPLC to determine the configuration of the product alcohol. Cultures capable of reducing the ketone of formula II at 1.0 g/l in high enantiomeric excess yielding the hydroxy compound of formula I
- 15 (the *S* enantiomer), are summarized in Table 1.

Table 1. Microorganisms capable of selectively reducing Compound II to Compound I at 1.0 g/l.

Culture	Strain #	% EE, S/R	% Yield
<i>Aspergillus niveus</i>	12276	100 <i>S</i>	7
<i>Curvularia lunata</i>	34477	100 <i>S</i>	18
<i>Mucor racemosus</i>	7924	100 <i>S</i>	4
<i>Mucor circinelloides</i>	1207a	100 <i>S</i>	9
<i>Saccharomyces cerevisiae</i>	Y-2034	100 <i>S</i>	8
<i>Saccharomyces uvarum</i>	10613	100 <i>S</i>	11
	32634	100 <i>S</i>	7
<i>Pichia methanolitica</i>	58403	84 <i>S</i>	24
<i>Torulaspora fermentati</i>	20100	100 <i>S</i>	5
<i>Torulaspora species</i>	66815	100 <i>S</i>	14
<i>Neurospora crassa</i>	14692	76 <i>S</i>	4
<i>Rhodococcus erythropolis</i>	25544	100 <i>S</i>	6
<i>Rhodococcus fascians</i>	202210	100 <i>S</i>	46
<i>Rhodococcus rhodochrous</i>	999	100 <i>S</i>	12
	21243	100 <i>S</i>	12
	29670	100 <i>S</i>	13
	29675	100 <i>S</i>	8

-7-

Table 2. Effect of bioconversion parameters on productivity of *R. fascians* ATCC No. 202210.

Seed Propagation conditions: 30°C, 250 rpm	Bioconversion Conditions (25 ml media/125 ml flask, 250 rpm)	% Yield
25 ml NYC /125 ml flask 24 hours (4% v/v transfer)	1 g/l: YPD, 30°C	41
	2 g/l: YPD, 30°C	32
25 ml YPD /125 ml flask 24 hours (4% v/v transfer)	1 g/l: YPD, 30°C	50
	2 g/l: YPD, 30°C	42
25 ml NYC /125 ml flask 72 hours (4% v/v transfer)	1 g/l: NYC, 25°C	45
	1 g/l: NYC, 30°C	42
	1 g/l: YPD, 30°C	47
	1 g/l: NYC, 35°C	48
	2 g/l: NYC, 25°C	44
	2 g/l: NYC, 30°C	43
	2 g/l: YPD, 30°C	44
	2 g/l: NYC, 35°C	39
25 ml TGP /125 ml flask 24 hours (4% v/v transfer)	1 g/l: TGP, 30°C	69
	2 g/l: TGP, 30°C	64
	4 g/l: TGP, 30°C	28
	10 g/l: TGP, 30°C	11
25 ml TGP /125 ml flask 24 hours (4% v/v transfer)	4 g/l: 5X cell concentrate, TGP, 30°C	68
	10 g/l: 5X cell concentrate, TGP, 30°C	31

Ketone compound of formula II dissolved in ethanol (25-50 mg/ml) added at 1-10 g/l where indicated following 24 hours of growth.

5

Table 3. Effect of bioconversion parameters on productivity of *G. candidum* ATCC No. 74487.

Seed Propagation conditions	Bioconversion Conditions (25 ml media/125 ml flask)	% Yield
25 ml SIM-6 /125 ml flask, 30°C, 250 rpm 72 hours (4% v/v transfer)	2 g/l: TGP, 30°C	18
	4 g/l: TGP, 30°C	9
	10 g/l: TGP, 30°C	6
	2 g/l: YPD, 30°C	33
	2 g/l: YPD, 35°C	39
	2 g/l: TNC, 30°C	38
	2 g/l: TNC, 35°C	45
	2 g/l: TN2C, 30°C	54
	2 g/l: TN2C, 35°C	46

Ketone compound of formula II dissolved in DMSO (25-50 mg/ml) added at 2-10 g/l following 24-48 hours of growth. TNC medium: 1% Tastone 154, 2% NZ-amine, 3% cerelose, pH 5.5. TN2C medium: TNC medium with 6% cerelose.

10

Example 3

Milligram quantities of the hydroxy compound of formula I derived from the stereoselective reduction of ketone compound of formula II were prepared using *Rhodococcus fascians* ATCC No. 202210 and fungal isolate *Geotrichum candidum* ATCC No. 74487 in multiple flask fermentations employing conditions summarized in Tables 2 and 3. Following 72-96 hours of incubation, fermentation broths of each of the cultures were pooled prior to centrifugation to isolate the cells which harbor most of the product and residual substrate. The cell pellets were extracted with TBME (10-20 volumes/wet weight). Anhydrous MgSO_4 was added to the TBME extract to remove residual water, the extract was filtered and the filtrate concentrated by evaporation.

Extract concentrate was subjected to purification by preparative thin layer chromatography employing 10-20 GF silica plates (20cm X 20cm X 1000 micron) and developed with a solution of EtOAc:hexane (50:50). Material comigrating with the desired product was scraped from each of the silica plates, pooled and eluted from the silica with TBME which was subsequently evaporated to dryness. Approximately 170 mg of product derived from 450-600 mg of ketone compound of formula II was isolated from each culture bioconversion. Isolated material was confirmed to be the desired hydroxy compound of formula I by reverse phase and chiral HPLC, NMR, and mass spectrum analyses.

WHAT IS CLAIMED IS:

1. A process for the stereoselective reduction of 1-(4-fluorophenyl)-
3(R)-[3-oxo-3-(4-fluorophenyl)propyl]-4(S)-(4-hydroxyphenyl)-2-
azetidinone to 1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)-
propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone comprising adding 1-(4-
fluoro-phenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)-propyl]-4(S)-(4-
hydroxyphenyl)-2-azetidinone to a microorganism in medium, medium
and buffer, medium and solvent, or medium and a mixture of buffer and
solvent, incubating the resulting mixture, and isolating 1-(4-fluoro-
phenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)-propyl]-4(S)-(4-
hydroxyphenyl)-2-azetidinone.
2. A process of claim 1 wherein the microorganism is of the genera
selected from the group consisting of *Aspergillus*, *Curvularia*,
Doratomyces, *Geotrichum*, *Mortierella*, *Mucor*, *Saccharomyces*,
Scytalidium, *Pichia*, *Torulaspora*, *Neurospora* and *Rhodococcus*.
3. A process of claim 2 wherein the microorganism is of the species
selected from the group consisting of *Aspergillus niveus*, *Curvularia*
lunata, *Doratomyces stemonitis*, *Geotrichum candidum*, *Mortierella*
isabellina, *Mucor racemosus* and *circinelloides*, *Saccharomyces*
cerevisiae and *uvarum*, *Scytalidium lignicola*, *Pichia methanolitica*,
Torulaspora fermentati and species, *Neurospora crassa* and
Rhodococcus erythropolis, *fasciens*, *rhodochrous* and species.
4. A process of claim 3 wherein the microorganism is *Rhodococcus*
fascians ATCC No. 202210 or fungal isolate *Geotrichum candidum*
ATCC No. 74487.
5. A process of claim 4 wherein the microorganism is
Rhodococcus fascians ATCC No. 202210.

INTERNATIONAL SEARCH REPORT

		Inter nal Application No PCT/US 99/07445
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12P17/10 C07D205/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12P C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Section Ch, Week 198632 Derwent Publications Ltd., London, GB; Class B03, AN 1986-208964 XP002123973 & JP 61 141894 A (SANKYO CO LTD), 28 June 1986 (1986-06-28)	1-3
A	abstract	4,5
Y	SANTANIELLO E. ET AL.: "The Biocatalytic Approach to the Preparation of Enantiomerically Pure Chiral Building Blocks." CHEM. REV., vol. 92, 1992, pages 1071-1087, XP002123971	1-3
A	the whole document	4,5
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
26 November 1999		15/12/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Douschan, K

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07445

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BELAN A. ET AL.: "Use of Biological Systems for the Preparation of Chiral Molecules." J. ORG. CHEM., vol. 52, 1987, pages 256-260, XP002123972	1-3
A	the whole document	4,5
Y	WO 97 16424 A (SCHERING CORP.) 9 May 1997 (1997-05-09)	1-3
A	page 2 -page 3; claim 1	4,5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Patent Application No

PCT/US 99/07445

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 61141894 A	28-06-1986	JP 1808579 C JP 5020069 B	10-12-1993 18-03-1993
WO 9716424 A	09-05-1997	AU 7472896 A US 5856473 A	22-05-1997 05-01-1999

THIS PAGE BLANK (USPTO)